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ORIGINAL ARTICLE

Phase II study of S-1 and docetaxel for previously treated patients with locally advanced or metastatic non-small cell lung cancer

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Abstract

Purpose The purpose of the present phase II study was to evaluate both the efficacy and toxicity of the combination of S-1 and docetaxel in previously treated patients with locally advanced or metastatic non-small cell lung cancer.

Methods Thirty-eight previously treated patients with non-small cell lung cancer were treated with S-1 (80 mg/m^2, days 1–14, oral) and docetaxel (40 mg/m^2, day 1, intravenous) every 3 weeks.

Results No complete response was observed, and seven patients had a partial response, yielding an overall response rate of 18.4% (95% CI, 7.7-34.3%). The median overall survival time and 1-year overall survival rate were 16.1 months and 60%, respectively. The median progression-free survival time was 4.4 months. Myelosuppression was the main toxicity with grade 3 or 4 neutropenia and leukopenia in 50% and 21%, respectively. There was no irreversible toxicity in this study.

Conclusions The combination of S-1 and docetaxel is well tolerable and has substantial activity for patients with locally advanced or metastatic non-small cell lung cancer. A phase III trial comparing docetaxel with or without S-1 would warrant further investigation.

Key words

non-small cell lung cancer, phase II study, docetaxel, S-1, second-line chemotherapy, third-line chemotherapy

Introduction

Non-small cell lung cancer (NSCLC) is a leading cause of cancer deaths worldwide, but only a minority of patients is amenable to surgical or definitive chemoradiotherapy. The overall prognosis of NSCLC patients remains poor; only 15.2% patients are alive after 5 years [1]. Almost all patients eventually experience progression during or after treatment. Second-line chemotherapy with docetaxel showed modest antitumor activity, with overall response rate (ORR) of 6.7-7.1%, and can prolong survival after failure of platinum-based regimens for NSCLC, with a 1-year overall survival (OS) rate of 21–31% [2, 3]. However, despite current evidences supporting the use of second-line chemotherapy, the modest survival benefits, the negligible low response rate and relevant toxicity may reduce the role of second-line chemotherapy in clinical settings.

S-1 (Taiho Pharmaceutical Co., Ltd.,, Tokyo, Japan) is an oral fluoropyrimidine agent comprising the 5-fluorouracil (5-FU) prodrug tegafur and two enzyme inhibitors, 5-chloro-2,4-dihydroxypyrimidine (CDHP) and potassium oxonate (OXO), in a molar ratio of 1:0.4:1. CDHP enhances the serum 5-FU concentration by competitive inhibition of dihydropyrimidine dehydrogenase (DPD), an enzyme responsible for 5-FU catabolism. OXO is a reversible competitive inhibitor of orotate phosphoribosyl transferase (OPRT),

a phosphoenzyme for 5-FU and reduces the gastrointestinal toxicity of 5-FU [4]. These mechanisms mean that oral S-1 administration can generate a higher concentration of 5-FU than protracted intravenous injection of 5-FU alone, while the incidence of toxicity in the gastrointestinal tract does not increase.

The combination of S-1 and docetaxel holds particularly great promise because both drugs have substantial antitumor activity as single agents, and they have different mechanisms of action and different toxicity profiles [2, 3, 5–7]. Recent preclinical studies have shown that S-1 has synergistic effects in human cancer xenografts [8–10]. The low level of DPD, thymidylate synthase activities, and a high level of OPRT activity enhance the antitumor effect of 5-FU and S-1. Docetaxel is one of the agents that modulate these enzyme expressions and activities. A phase I/II study has shown that this combination was well tolerated with moderate toxicities and promising activity in patients with gastric cancer [11]. Therefore, we conducted a phase II study to evaluate both the efficacy and toxicity of S-1 combined with docetaxel in previously treated patients with locally advanced or metastatic NSCLC.

Materials and methods

Eligibility criteria

Eligible patients were aged 20–74 years and had histologically or cytologically confirmed locally advanced or metastatic NSCLC (stages IIIB–IV or relapse after surgery) that progressed after first- or second-line chemotherapy or chemoradiotherapy. The patients were required to have measurable disease by the Response Evaluation Criteria in Solid Tumors (RECIST), an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1, ability to take oral medication and normal ECG. Eligibility requirements also included a white blood cell count of ≤12,000 cells/mL, an absolute neutrophil count of ≥2000 cells/mL, a platelet count of ≥100,000 cells/mL, a hemoglobin level of ≥9 g/dL, a serum total bilirubin level of ≤1.5 mg/dL, a serum aspartate aminotransferase (AST)/alanine aminotransferase (ALT) of less than or equal to twice the upper limit of normal, a serum creatinine level of ≤1.5 mg/dL and a normal electrocardiogram. Prior thoracic radiotherapy was allowed as long as it had been completed at least 12 weeks prior to inclusion and the patient had recovered from any toxicity. At least 4 weeks had to have elapsed from prior surgery and completion of prior chemotherapy or chemoradiotherapy. Patients who had exhibited evidence of severe heart or pulmonary disease or concomitant malignancy were excluded. The protocol was approved by the Ethics Committee of Kyoto University, and every patient gave written

informed consent. This trial was registered at University hospital Medical Information Network, Japan (protocol ID number, UMIN000000501 at http://www.umin.ac.jp/).

Treatment plan

S-1 was given orally twice daily for 2 weeks, followed by a drug-free interval of 1 week (one cycle). Dose of S-1 administered each time was calculated according to the patient's body surface area as follows: less than 1.25m^2, 40mg; 1.25-1.5m^2, 50mg; and greater than 1.5m^2, 60mg. Docetaxel intravenous infusion (40 mg/m^2) was administered on day 1. The treatment regimen was repeated every 3 weeks until disease progression or intolerable toxicity occurred. For patients who experienced febrile neutropenia, hemorrhage with grade 3 or 4 thrombocytopenia, or grade 3 or 4 non-hematologic toxicity, the dose of docetaxel was to be reduced to 35 mg/m^2 and the dose of S-1 was also to be reduced to 80% of the initial dose. For patients who still experienced the same toxicity after the dose reduction, S-1 was to be reduced to 80% of the reduced dose, and this could be done up to twice. If recovery from such toxicities at a reduced dose was confirmed, administration at the reduced dose was continued. Patients who still experienced the same toxicity after the dose reduction were to be withdrawn from the study treatment.

Evaluation of response and toxicity

Patients underwent tumor assessments at baseline and every 6 weeks by investigators using RECIST. Patient survival was observed until death, loss to follow up, or study closure. Adverse events were recorded using the National Cancer Institute Common Terminology Criteria for Adverse Events (version 3).

Statistical analysis

The primary end point was the ORR as assessed in all eligible and treated patients, with success being defined as a complete response (CR) or partial response (PR) according to RECIST. The secondary endpoints were OS, progression-free survival (PFS) and adverse events. The design of this study was based on a binomial distribution with no planned interim analysis. Assuming a null hypothesis of a 9% ORR and an alternative hypothesis of a 25% ORR, with one-sided type I error=0.1 and type II error=0.1, it was necessary to enroll a minimum of 35 patients. According to this, we aimed for 40 patients to take non-evaluable patients into consideration.

Exact confidence interval (CI) and exact P-value for ORR were based on the binomial distribution. OS was calculated from the date of registration until death from

any cause, whereas PFS until disease progression or death from any cause. OS and PFS were analyzed using the Kaplan–Meier method. All statistical tests were one-sided, and a P-value of less than 0.05 was considered statistically significant. All analyses were performed using SAS version 9.1.3 (SAS Institute, Cary, NC, USA).

Results

Patient characteristics

Between August 2006 and December 2007, 42 patients were enrolled in this study according to the eligibility criteria. Thirty-nine of these 42 patients were eligible, of the remainder one patient had stage IIIA NSCLC and two patients were without adequate liver function. Following the study protocol, one eligible but untreated patient was excluded from the analysis because of the incidence of a compression fracture caused by osteoporosis before treatment. Baseline characteristics of the 38 patients are summarized in Table 1. The median age was 65 years (range, 44–74 years). The majority of patients had an ECOG PS of 0 (95%), had been histologically or cytologically diagnosed as having adenocarcinoma (79%) and had progressed after at least one previous platinum-based chemotherapy regimen (92%). The median number of courses administered per patient was five (range, 1–8). The median follow-up time was 17.2

months.

Efficacy

Tumor response results are shown in Table 2. Among all treated patients, no CR was observed and seven patients had a PR, yielding an ORR of 18.4% (95% CI, 7.7–34.3%; P=0.05 under the null hypothesis of a 9% ORR). Among the patients with adenocarcinoma, PR was observed in 4/30 (13.3%). As shown in Figure 1, the median OS time was 16.1 months and the 1-year OS rate was 60% (95% CI, 42.5–73.6%). The 1-year OS rates in stage-IIIB patients, stage-IV patients and patients with relapse after surgery were 70, 42 and 80%, respectively. The median PFS time was 4.4 months, and the 1-year PFS rate was 37% (Figure 1).

Safety

The major adverse events are shown in Table 3. The most frequent hematological toxicity was neutropenia with grade 3 or 4 neutropenia observed in 50% of patients. Of these events, grade 4 neutropenia was observed in seven patients (18%) and febrile neutropenia in one patient (3%). Grade 3 or 4 leukopenia was reported in 21% of patients. The non-hematological grade 3 toxicities were anorexia in five patients

(13%), stomatitis in four patients (11%), hand-foot skin syndrome in two patients (5%), diarrhea in two patients (5%) and vomiting in one patient (3%). There was no death or irreversible toxicity in this study that was considered to be related to treatment.

Discussion

Almost all patients with advanced NSCLC treated with first-line chemotherapy experience progression, and current options for the second-line treatment of NSCLC include single-agent chemotherapy with docetaxel, pemetrexed or erlotinib [12], which large-scale randomized clinical trials indicate as the standard regimen. However, the clinical responses to these agents are of short duration, and the survival benefit is limited.

Many reports have been published investigating combination chemotherapy using two non-platinum agents for recurrent NSCLC in randomized clinical trials, with the objective of improving outcomes further. However, none of these studies have demonstrated improved survival with combination chemotherapy, whereas there have been relatively higher or intolerable toxicities [13–16]. Therefore, more active regimens

for the second-line chemotherapy are much needed.

In the present study, we evaluated the efficacy and safety of the combination of S-1 and docetaxel, two agents that separately have shown promise in the treatment of advanced or metastatic NSCLC. This combination chemotherapy conferred efficacy with an ORR of 18%, a median OS time of 16 months and a 1-year OS rate of 60%. The 18% ORR observed in this study was slightly lower than expected. However, the survival benefits as second- or third-line therapy observed compare favorably with other chemotherapy regimens, such as monotherapy with docetaxel (6–14 months) [2, 3, 7], pemetrexed (8 months) [17], erlotinib (6–15 months) [18–20] or oral topotecan (6–8 months) [21, 22], or combination chemotherapy of irinotecan and cisplatin (11 months) [23], or oral fluoropyrimidine UFUR and gemcitabine (13 months) [24], although between-study comparisons should be made with caution.

Prolonged survival may be due to substantial post-study treatment, especially epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs). Although EGFR mutation status was not analyzed in this study, 17 patients received EGFR-TKIs and 9 of those patients for over a month.

The hematological toxicity observed here was minimal and tolerable, despite the fact that grade 3 or 4 neutropenia occurred in 50%, which is comparable with the

toxicity caused by docetaxel monotherapy. The majority of non-hematologic toxicities were mild and tolerable without grade 4 non-hematologic toxicity. These toxicity results are consistent with those observed in a phase I/II study in patients with gastric cancer [11].

During the preparation of this manuscript, Atagi et al. [25] reported the results of a phase I/II study, in which the combination of S-1 and docetaxel was evaluated for patients who had failed one or more prior chemotherapy regimens. In the phase II part of their study, seven of 29 eligible patients achieved a PR, yielding an ORR of 24%, with a median OS time and the 1-year OS rate of 12 months and 42%, respectively. Patient characteristics were similar except for stage and ECOG PS: fewer patients who had experienced relapse after surgery were included, and 31% and 69% patients had ECOG PS of 0 and 1, respectively, in the study by Atagi et al. [25]. Although these differences in patient characteristics may lead to more favorable survival results in our study, the combination of S-1 and docetaxel still seems to be consistently promising as a chemotherapy option after the failure of prior chemotherapy for advanced NSCLC.

In this study, the dose of docetaxel was lower than that commonly used in docetaxel monotherapy. As a second-line docetaxel monotherapy, a dose of 75 mg/m^2 every 3 weeks is used in the United States and Europe, and the dose is 60 mg/m^2 every 3

weeks in Japan. However, our regimen is widely recognized as a tolerable and optimized combination of S-1 and docetaxel in gastric cancer [11], and thus, also in lung cancer, it is considered promising in terms of toxicity and efficacy. Furthermore, it was the recommended dose in the phase I part of study reported by Atagi et al. [25].

There are many report of ethnic differences in the safety and efficacy profile of S-1 and docetaxel [25–28], and it is shown that CYP2A6*9 genetic polymorphism is a potential predictive marker, for efficacy and toxicity, for the patients received the combination of S-1 and docetaxel for metastatic gastric carcinoma [29]. In the development of a S-1/docetaxel combination therapy in the United States and Europe, further optimization of the dose of each agent may be required to account for these differences.

In conclusion, the combination of S-1 and docetaxel is well tolerable and promisingly effective for patients with locally advanced or metastatic NSCLC. A phase III trial comparing docetaxel with or without S-1 would warrant further investigation.

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Notes

KY, KY and MN equally contributed to this work.

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Table 1. Patient characteristics (*n*=38)

	No. of patients (%)
Median age	65 years; range, 44–74 years
Gender	
Male	23 (61%)
Female	15 (40%)
Histology	
Adenocarcinoma	30 (79%)
Squamous Cell Carcinoma	4 (11%)
Others	4 (11%)
Stage	
IIIB	10 (26%)
IV	18 (47%)
Relapse after surgery	10 (26%)
IIIB[a]	3 (8%)
IV[a]	7 (18%)
ECOG PS	

0	36 (95%)
1	2 (5%)
Smoking history	
Current/Former	24 (63%)
Never	14 (37%)
Number of previous chemotherapy regimens	
1	23 (61%)
2	15 (39%)
Previous chemotherapy	
Platinum-containing	35 (92%)
Gefitinib	7 (18%)

ECOG PS, Eastern Cooperative Oncology Group performance status.

[a]Restaging after relapse.

Table 2. Overall response rates according to RECIST (*n*=38)

CR	PR	SD	PD	NE	ORR
0	7	25	6	0	18.4% (95% CI, 7.7–34.3%)

RECIST response evaluation criteria in solid tumors, *CR* complete response, *PR* partial response, *SD* stable disease, *PD* progressive disease, *NE* not evaluable, *ORR* overall response rate, *CI* confidence interval.

Table 3. Adverse effects according to National Cancer Institute Common Terminology Criteria for Adverse Events (version 3) (*n*=38)

Toxicity	All grades		Grade 3 or 4	
	No.	(%)	No.	(%)
Hematological toxicity				
Neutropenia	31	(82%)	19	(50%)
Leukopenia	22	(58%)	8	(21%)
Anemia	18	(47%)	1	(3%)
Thrombocytopenia	3	(8%)	0	
Febrile neutropenia[a]	1	(3%)	1	(3%)
Gastrointestinal toxicity				
Stomatitis	33	(87%)	4	(11%)
Nausea	17	(45%)	0	
Vomiting	7	(18%)	1	(3%)
Diarrhea	2	(5%)	2	(5%)
Metabolic/Laboratory				
AST	15	(39%)	0	

Hyperbilirubinemia	10	(26%)	1	(3%)
ALT	10	(26%)	0	
Hypercreatinemia	3	(8%)	0	
Other toxicity				
Anorexia	25	(66%)	5	(13%)
Hand-foot skin reaction	25	(66%)	2	(5%)
Fatigue	24	(63%)	0	
Hyperpigmentation	8	(21%)	-	
Weight loss	4	(11%)	0	
Pneumonitis	2	(5%)	0	

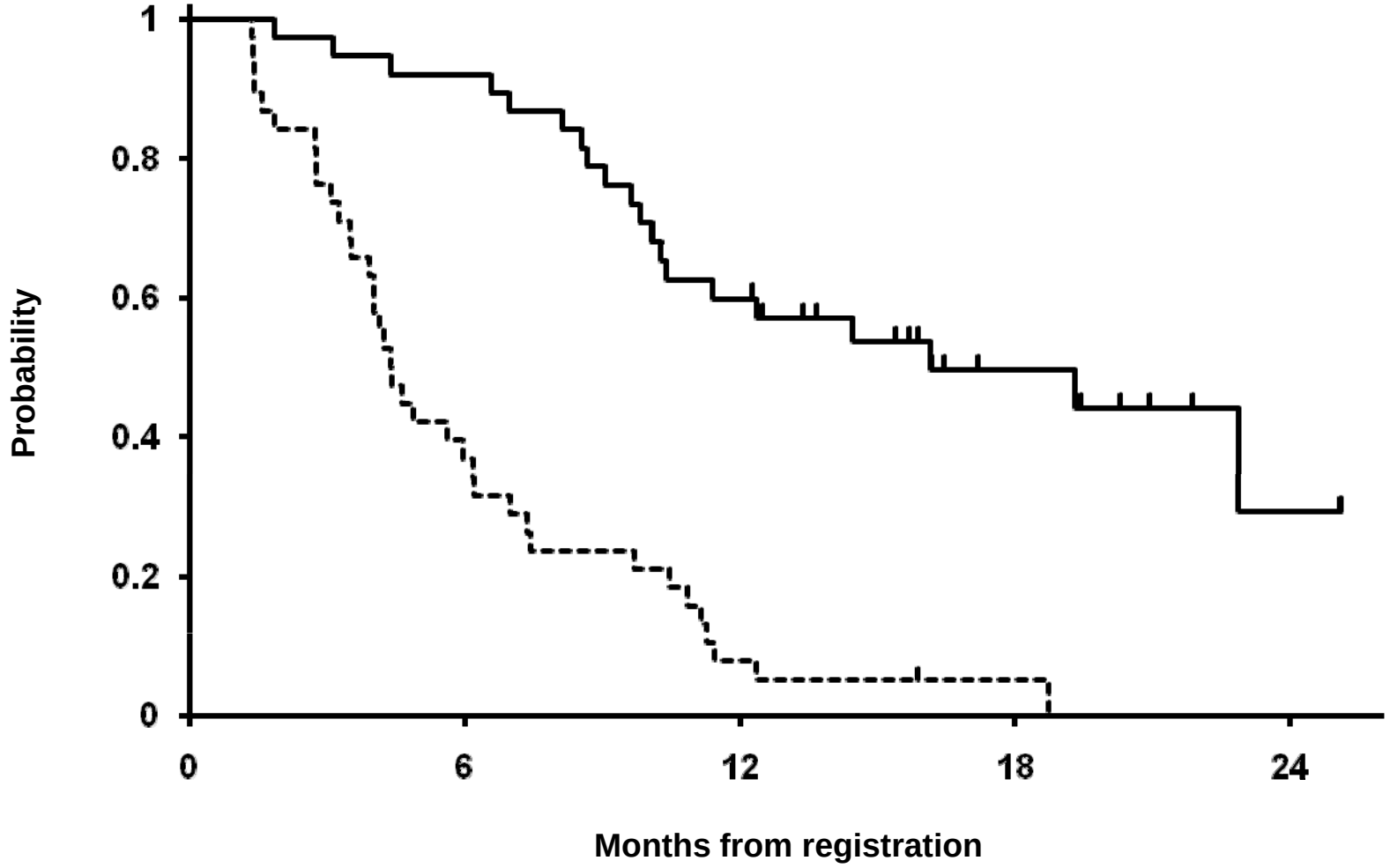
AST, aspartate aminotransferase; ALT, alanine aminotransferase.

[a]Fever with concomitant grade 3 or 4 neutropenia.

Legend for the figure

Figure 1: Kaplan–Meier survival curves demonstrating overall (*solid line*) and progression-free (*dashed line*) survival. *OS* overall survival, *PFS* progression-free survival

Figure 1



 # Patients at risk

Months	0	6	12	18	24
OS	38	35	22	9	2
PFS	38	14	3	1	0